3 Medical management of the deceased donor in solid organ transplantation

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As waiting lists for each of the solid organs continue to lengthen, various strategies have emerged to combat the evolving dilemma of increased demand with a relatively stagnant supply. These include a spectrum of programs targeting the general population, ranging from public service initiatives designed to educate people about the dire need for organ donation to legislative programs aimed at simplifying processes for people to identify themselves as potential donors in the case of a catastrophic medical emergency. As surgical and medical techniques continue to advance, there has been ongoing re-evaluation of organ-specific donor criteria, attempting to optimize use of donors previously deemed unsuitable due to age or specific medical criteria. The last few years also have shown significant progress in the use of traditionally unacceptable classes of donors, such as those donating after cardiac death (DCD), as potential donation candidates. However, one of the largest and most readily available pools of potential organ donors, continually underappreciated in many hospitals, remain those patients who expire within their own intensive care units (ICUs). Many of these will have undergone extensive diagnostic and therapeutic evaluations, having never been recognized as reasonable candidates. When including the additional number of individuals who have been identified as potential candidates but sustain cardiovascular collapse and somatic cell death during the ensuing evaluation, before any actual procurement procedure, the number of missed donation opportunities is further increased.

For any patients who sustain a serious injury or illness, the initial approach focuses on attempts to restore them to their premorbid state. Whether the result of unexpected trauma in a previously healthy individual, or a new illness in the setting of someone with co-morbidities, each evaluation consists of the appropriate diagnostic studies and therapeutic interventions, provided in an efficient and expedited manner. At the time of initial presentation, either in the emergency room or shortly after arrival in the ICU, a small minority of patients will already have sustained a catastrophic injury to the central nervous system (CNS) and meet criteria for brain death. In this setting, candidacy for organ donation should be assessed immediately. If there is an absolute contraindication to their candidacy as a donor, or if the patient's representative refuses to consent to donation, life support should be withdrawn once the family has had an appropriate opportunity to gather and pay their respects.

A much larger portion of patients will present to critical care units with less severe levels of injury or illness. Each of these individuals will undergo the appropriate diagnostic evaluation specific to the unique circumstances and targeted therapeutic modalities will be initiated. Through advances in supportive care and monitoring techniques, it is now commonplace for individuals to survive illnesses that were historically thought to be fatal. Although these advances have yielded incredible results, a portion of

Primer on Transplantation, 3rd edition.
Edited by Donald Hricik.

these patients will still deteriorate and their inciting illness will ultimately prove to be fatal. Within the busy environment of a modern ICU, with complicated patient profiles and rapidly evolving hemodynamic derangements, it is crucial that appropriate surveillance protocols be employed to monitor those individuals who may represent potential organ donors.

For any individual, up until the point that a formal diagnosis of brain death has been declared, all aspects of patient care are focused on restoring the patient to the premorbid state. Utilizing pre-existing advanced directives, combined with serial discussions with family representatives when the patient is unable to adequately participate, an individualized care plan is formulated and then updated as changes to the patient's condition occur. The variable course for any individual patient through a catastrophic illness or injury must be recognized. It is crucial that appropriate surveillance and monitoring programs be well established in each center to identify those patients in whom evolving injury to the CNS is likely to proceed to brain death. Clinical triggers and notification of the local organ procurement organization (OPO) about those patients with a high likelihood of progression to brain death is a key component in any screening protocol. This assists the OPO and local transplant centers in the event that brain death is declared. It is crucial, during this entire process, that the needs of the individual patient and familial support are the focus. Establishing this framework assists with the ensuing discussions if the clinical situation deteriorates.

The bulk of this chapter deals with medical management of the brain-dead deceased donor. Non-heart-beating donors (i.e., DCDs) represent a growing proportion of deceased donors. Their management is addressed at the end of the chapter.

Declaration of brain death

Our understanding of brain death, from both an anatomical and a pathophysiologic perspective, has greatly evolved since the first description in 1959 by Mollaret and Goulon. *Le coma depasse*, literally termed "irreversible coma," represented a series of comatose patients with absent brain-stem reflexes, lack of respirations, and absence of electroencephalographic (EEG) activity. This description remains the mainstay of criteria for brain death as accepted both medically and legally today. Medical, legal, and bioethical issues related to declaration of brain death were first formally discussed through an ad hoc committee at Harvard Medical School in 1968 and further examined through the Conference of the Medical Royal Colleges and Faculties in the UK in 1976. In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published definitions clarifying specific criteria equating brain death with cardiovascular death.

During this same time period, the technical aspects of routine ICU care have evolved tremendously, making it possible to invasively support virtually every organ system. From advancements in hemodynamic monitoring and ventilator strategies to extracorporeal renal replacement therapy, the ability to maintain somatic cell function in the setting of severe neurologic compromise for indefinite periods of time is now possible. There is a much greater understanding of the physiologic changes that accompany severe brain injuries that lead to elevated intracranial pressures and ultimately herniation of the brain stem through the foramen ovale. The natural protective strategy is to maintain the perfusion of the CNS. In the setting of increased intracranial pressure, whether induced by hemorrhage, edema, a mass, or any other space-occupying process, the compensatory strategy is to elevate mean arterial pressure to maximize end-organ tissue perfusion. In this light, each of the pathophysiologic processes observed as a patient with catastrophic injury to the CNS evolves to actual brain death represents failed attempts at maintaining perfusion. Within this context, it is essential that each person participating in the care of patients within an ICU has a clear understanding of the criteria for the declaration of brain death. It is also important to note that there may be local variances in the declaration process. Information of both state and local requirements should be available in every ICU.

Briefly, the declaration of brain death requires detailed examination, demonstrating the loss of all brain function in the appropriate clinical setting without confounding variables. This begins with a detailed neurological examination of the comatose patient demonstrating loss of all reaction to painful

stimuli in all four extremities. This is followed by careful examination for the loss of all brain-stem functions, including oculocephalic, vestibular, corneal, pupillary, and gag reflexes. This examination must occur in the appropriate clinical setting with an injury or illness pattern compatible with the degree of central nervous compromise encountered and appropriate radiographic findings. Equally important is the verification of any confounding variables that may interfere with the clinical examination. These include, but are not limited to, drug intoxications, severe electrolyte or endocrine disturbances, extreme temperature derangements, or the administration of sedatives, hypnotics, or neuromuscular paralyzing agents. There is no uniformly accepted standard for the qualifications of those performing this examination. In some locales, this examination must be repeated on two occasions with a certain waiting time between examinations. In others, two examinations performed at the same time by different qualified providers will suffice. Knowledge of accepted local practices is required.

Once confounding variables have been excluded, coma is established, and brain-stem function is absent, the next step involves performing an apnea test and assessing the patient's response to hypercapnia. An apnea test is performed by preoxygenating the individual on 100% FiO_2 (inspired oxygen fraction). A baseline arterial blood gas is then obtained and the patient is removed from mechanical ventilation. At some centers, the patient is maintained on 100% FiO_2 and continuous positive airway pressure (CPAP); at others, the patient is removed from the ventilatory circuit and an oxygen catheter is inserted through the endotracheal tube to the carina where 6–12 L of oxygen are delivered. In either protocol, it is essential that the patient does not receive any ventilatory support. The patient is then observed for any evidence of spontaneous respiratory effort. If there is any effort such as chest movement, the test is terminated and the patient, although severely injured, does not meet the criteria for brain death. Assuming that there are no signs of respiratory effort, after 8–10 min an arterial blood gas is obtained for reassessment of the gas tension of carbon dioxide (PCO_2). A PCO_2 > 8 kPa (>60 mmHg) demonstrates the patient's inability to respond to hypercapnia and is consistent with brain death. If the PCO_2 has not risen above 8 kPa (60 mmHg), the test should be repeated for an extended period of time. In the setting of an elevated baseline PCO_2, such as may be seen in underlying lung disease, a positive test is typically described as a rise of >4 kPa (20 mmHg) in PCO_2 above the baseline. If the patient develops hemodynamic instability or profound hypoxia during testing, typically defined as saturations <85% monitored by pulse oximetry, an arterial blood gas should be immediately obtained and the patient placed back on mechanical ventilation. If the above criteria are fulfilled, then the test is considered positive.

Key points 3.1 Elements of a positive apnea test in determination of brain death

Removal from respirator:

Continued administration of oxygen

Absence of chest movements

After 8–10 min, PCO_2 8 kPa (>60 mmHg) or >4 kPa (>20 mmHg) above baseline if previously hypercapnic

Patients who have a clinical examination consistent with brain death in the absence of any confounding issues and a positive apnea test are declared brain dead. The inability to perform any part of the physical examination such as a full cranial nerve examination due to facial injury or instability during apnea testing mandates a confirmatory test. There are four currently accepted confirmatory tests for the diagnosis of brain death and any of the four can be employed based on local resource availability and physician preference; they include an EEG demonstrating the absence of electrical activity, a technetium (^{99m}Tc) brain scan showing lack of uptake in the brain parenchyma (the "hollow skull" sign), transcranial Doppler sonography demonstrating lack of diastolic or reverberating flow, or cerebral angiography revealing lack of flow at the carotid bifurcation and circle of Willis. As discussed above, with very rare religious exceptions, it is now widely accepted that a formal declaration of brain death is equivalent to cardiovascular death. In the scenario where organ donation will not be pursued, the family should be given the opportunity to gather and pay their respects before the termination of life support, but, legally, the patient has already expired.

In the scenario where a patient is pronounced brain dead and a possible organ donor, care should be directed toward maintenance of the potentially transplantable organs. During the evaluation period, the basic axioms of critical care guide therapy. In many circumstances, the initial resuscitation of a potential donor involves correction of severe volume, acid–base, and electrolyte abnormalities that have evolved during the failed therapeutic attempts to combat an elevated intracranial pressure. It is not uncommon for patients to be markedly volume depleted and/or severely hypernatremic as a consequence of CNS-protective strategies such as use of mannitol or other osmotic diuretic agents. In many institutions, there is a natural tendency to diminish the intensity of support in this patient population. However, the need for aggressive ICU level monitoring and support is imperative to prevent hemodynamic collapse and cardiac arrest before organ procurement can be undertaken. This time period immediately after brain death is marked by intense hemodynamic instability related to the combined effects of the initial injury, the resuscitative effort, and the pathophysiologic effects of brain death. The processes leading to herniation of the brain, combined with the compensatory hemodynamic mechanisms that occur in an effort to maintain tissue perfusion, establish the framework of pathophysiology upon which the clinical care of the potential organ donor is based.

Consent for organ donation

To maximize the potential pool for organ donors, it is imperative that a uniform approach to consent exist for every person who expires. This is best accomplished through protocols using people trained in these discussions. As part of this process, it is crucial that families understand the definition of brain death. Although their loved one still has a palpable pulse and beating heart, he or she has expired, irrespective of any decisions re organ donation. Any decisions to participate in organ or tissue donation do not impact the timing of religious services or disfigure the body in a manner that precludes visitation and viewing customs. It is important to separate the process of brain death declaration from the request for organ donation in order to allow appropriate time for questions, grieving, and acceptance. There is tremendous variability in the conversion rate of potential donors to actual donors. Any protocol designed to improve this conversion must include components of surveillance to identify those patients likely to progress to brain death, a standardized protocol for the declaration of brain death, a uniform process of request for organ donation, and optimal medical management of all potential donors.

Case

A 21-year-old man sustained massive head trauma in a motor vehicle accident. Although his prognosis was grim at presentation, he initially exhibited spontaneous respirations precluding declaration of brain death. The bereaved family asked the nursing staff about possible organ donation but expressed concern about further mutilation of the body. A representative from the local organ procurement agency met with the family, spoke at length about the concept of brain death, and assured them that an organ procurement procedure would not interfere with viewing of the body or a funeral. Twelve hours later, the man was declared brain dead and the family consented to donation of all viable organs.

Physiology of brain death

Ischemia–reperfusion injury

The physiology of severe CNS injury, and the resultant pathology that is observed clinically is most consistent with ischemia-reperfusion injury. In the setting of elevated intracranial pressures, the rostral–caudal progression of ischemia resulting in herniation and brain death produces a predictable hemodynamic pattern. As the ischemia evolves to include the medulla oblongata, a profound autonomic surge of catecholamines develops in a final attempt to maintain cerebral perfusion pressures in the setting of increasing intracranial pressure. This catecholamine surge typically produces intense peripheral vasoconstriction and cardiac stimulation resulting in transient hypertension. After the subsequent brain-stem herniation and spinal denervation, there is deactivation of the sympathetic nervous system with the resultant vasodilation and reduced catecholamine levels. Unfortunately, this process results in a reduction in cardiac stimulation and hemodynamic instability. There is evolving

evidence, as described below, that this process leads to an intense ischemia–reperfusion injury, with an associated inflammatory response and further endothelial injury. As this process evolves, the contribution of injury to the neuroendocrine structures within the CNS may further impact the hemodynamic instability that is frequently encountered.

Hypothalamic–pituitary axis

To understand the compensatory mechanisms that develop in the setting of a significant injury to the CNS, a basic knowledge of the underlying anatomic structures is required. This is particularly important when considering the specific components of the hypothalamic–pituitary axis which regulates control of virtually every component of the endocrine system. Anatomically, the hypothalamus is located at the base of the brain between the optic chiasma and the third ventricle. Through the pituitary stalk, a complicated portal vascular network connects the median eminence of the hypothalamus and the anterior portion of the pituitary gland, which lies immediately outside the dura in the sella turcica. The pituitary gland itself develops from two distinct embryologic tissues, the adenohypophysis, or anterior pituitary, and the neurohypophysis, or posterior pituitary. The anterior pituitary is derived from the embryologic oral cavity within Rathke's pouch, whereas the posterior pituitary is formed from neural ectoderm of the embryologic forebrain. Although these two structures combine during early development to form the complete pituitary gland, they continue to retain distinctly different innervations, blood supplies, and hormone production. In this way, they can be thought of as two different endocrine structures.

The blood supply to the hypothalamus arises from the superior hypophyseal artery. The anterior pituitary itself does not actually have a direct arterial supply, instead receiving blood flow from the hypothalamus through the intricate vascular network described previously. The posterior pituitary receives its arterial blood supply through the inferior hypophyseal artery. The venous drainage is also distinctly different, through the petrosal sinuses, and ultimately the internal jugular vein for the anterior system, and through the inferior hypophyseal vein for the posterior pituitary.

This dual blood supply serves to emphasize a stark contrast between the hormone products and regulatory processes of the anterior and posterior pituitary structures. The anterior pituitary gland is isolated from the systemic circulation, receiving blood flow exclusively through the low-pressure, portal vasculature. The median eminence of the hypothalamus is thus able to exert precise control over the anterior pituitary through release of small peptide regulatory hormones without significant dilution or degradation within the systemic circulation. The close proximity of these structures also allows high concentrations of these mediators with relatively little production in a pulsatile fashion. Conversely, hormone regulation of the posterior pituitary occurs through direct neuronal connections from the hypothalamus, originating in the supraoptic and paraventricular nuclei. Many hormones produced in the anterior pituitary, including growth hormone, luteinizing hormone, adrenocorticotropic hormone, thyroid-stimulating hormone (TSH), follicle-stimulating hormone, melanocyte-stimulating hormone, and endorphins. The two primary hormones derived from the posterior pituitary are vasopressin and oxytocin. In total, these various hormones represent virtually every aspect of the human endocrine system and account for much of normal homeostasis. Any injury to the hypothalamic–pituitary axis, whether directly due to trauma, vascular insult, or infection, or indirectly through elevated intracranial pressures, can disrupt both the formation and release of these various hormones.

There has been conflicting data about the extent to which dysfunction of the hypothalamic–pituitary axis affects the hemodynamic instability in potential organ donors. In animal models, which typically include a model of brain death in which a balloon inserted into the cranium is suddenly expanded, there have been multiple studies demonstrating a decline in both anterior and posterior pituitary hormone levels. In human studies, the decline in pituitary hormone levels has been more inconsistent, likely reflective of the heterogeneity of the injury patterns and variability in the timing from actual brain death to the declaration process. In addition, there is mixed evidence from both animal and human studies demonstrating improvement in hemodynamic parameters after hormone supplementation. There is significant experimental and clinical evidence of posterior dysfunction

leading to vasopressin deficiency and diabetes insipidus. When this is manifest clinically by profound dilute diuresis in the setting of increased serum osmolarity, treatment with arginine vasopressin should be added to the regimen.

The issue of thyroid replacement in this setting has been the subject of debate. Although multiple studies have demonstrated low thyroxine (T_4) and TSH levels after brain death, in studies where reverse-triiodothyronine (rT_3) levels have been measured, the pattern is more consistent with "euthyroid sick syndrome." As T_4 has inotropic properties, it is not entirely clear whether the hemodynamic improvement after thyroid supplementation represents correction of endocrine dysfunction or simply augmented cardiac function. The role of adrenal insufficiency in potential organ donors and the effects of supplementation with exogenous glucocorticoids have also been controversial. Several studies have demonstrated improved hemodynamic parameters and improved conversion rates with utilization of hormonal replacement protocols. In potential organ donors with continued hemodynamic instability after appropriate volume replacement, it is reasonable to consider hormonal supplementation, typically consisting of a combination of T_4, glucocorticoids, and vasopressin.

Donor criteria

For each solid organ that can be transplanted, there are both general and organ-specific contraindications to donation. The absolute contraindications include a variety of infections, such as those with human immunodeficiency virus (HIV), prion-related diseases, human T-cell leukemia–lymphoma virus (HTLV), and systemic viral infections such as measles. Although bacteremia and fungemia will frequently preclude donation, they are not absolute contraindications and may be allowable in appropriate circumstances. Patients with active malignancies, with the exception of non-melanoma skin cancers and certain brain tumors, are not considered possible donors. In those with a history of malignancy, the duration of disease-free existence and cell type help determine possible candidacy.

The ideal donor for any organ is a previously healthy individual with an intense, abrupt, and isolated CNS injury with little systemic compromise. Such individuals constitute the vast minority of donors. Specific criteria for each organ system vary based on the organ in question. Arguably the organ system typically precluded due to specific donor criteria is the lung, representing the unique potential for injury or insult within the pulmonary system. With any significant CNS injury, there is the potential for aspiration due to difficulties with airway protection. In addition, in those potential donors with prolonged resuscitative efforts, there is potential for barotrauma, ventilator-associated infections, and iatrogenic complications that may all negatively impact the potential for donation. The ideal lung donor is aged less than 55 years, has a PaO_2/FiO_2 ratio > 300 on FiO_2 100% on 5 cmH_2O of PEEP (positive end-expiratory pressure), a clear chest radiograph with the absence of chest trauma, aspiration, purulent secretions, or malignancy, and a minimal smoking history. The appropriateness of these criteria has recently been challenged and attempts to increase the donor pool by expanding these criteria are under review. It is ultimately the responsibility of the OPO and directors of the transplant center to authorize the appropriateness of an individual donor.

Key points 3.2 Definition of an ideal lung donor

- Aged <55 years
- PaO_2/FiO_2 ratio of >300 on 5 cmH_2O of positive end-expiratory pressure
- Clear chest radiograph
- Smoking history <20 pack-years
- Absence of:
- Chest trauma
- Aspiration
- Purulent secretions
- Malignancy

Cardiovascular management

Consistent with the approach to management of any critically ill patient, a fundamental understanding of the physiology of the pertinent illness provides the basis for optimal management strategies. Donor management necessitates an ongoing level of intensity;

however, it is imperative that the focus ultimately shifts from cerebral protective strategies to optimizing donor organs for transplantation. In effect, this is the simultaneous medical management of organs for eight potential recipients. Cardiovascular management is the cornerstone of donor management and facilitates donor somatic survivorship, which ensures that all organs can be procured. Similarly, optimal hemodynamic management and adequate perfusion pressures maintain all organs to be procured in the best possible condition. Lastly, the recently recognized inflammatory response of brain death related to ischemia–reperfusion injury is proposed to initiate the development of an immunologic continuum between the donor and recipient. Optimal hemodynamic management mitigates ongoing ischemia–reperfusion injury which can facilitate better graft function in the recipient.

Contributing factors

Cardiovascular and hemodynamic dysfunctions encountered during management of the potential organ donor represent a continuum of cardiovascular injury that starts with the initial neurologic insult to the brain. It has long been recognized that severe neurologic injury produces cardiac dysfunction. Recognizing that the magnitude of injury in the non-survivor of severe brain injury is likely greater than in survivors, it seems plausible to assume that the cardiovascular dysfunction is similarly more severe and compounded by the physiologic effects of brain death, including profound levels of vasodilation and endocrine dysfunction. A non-aggressive approach to hemodynamic stabilization or an inability to maintain coronary perfusion pressure gradients will contribute to the hemodynamic instability of the potential organ donor.

Neurocardiac injury patterns reported in patients with subarachnoid hemorrhage illustrate the effects related to the initial insult particularly well. In this population, the magnitude of the neurologic injury assessed by the Hunt–Hess score is a significant predictor of the extent of myocardial necrosis and echocardiographic abnormalities seen after the precipitating event. It appears that the mechanism of injury is related to excessive sympathetic stimulation and release of catecholamines. Systolic impairment has been reported in 10–28% of patients and diastolic dysfunction has been observed in 70% of patients with subarachnoid hemorrhage. It is important to recognize that a significant percentage of surviving patients with cardiac dysfunction will recover left ventricular systolic function over time. Unfortunately, echocardiographic evidence of left ventricular dysfunction often precludes procurement of the heart for transplantation.

The impact of brain death on cardiovascular function was first recognized in the early 1980s by the cardiovascular transplantation group in South Africa (28). When comparing hearts that were taken from healthy anesthetized baboons to hearts taken from brain-dead donors, the investigators noted that there was appreciable dysfunction in the brain-dead donor hearts. The investigators speculated that the significant dysfunction was related to the physiology of brain death and subsequently characterized the physiology of brain death through a series of elegant experiments. That physiology is characterized by an initial intense sympathetic surge, termed the "autonomic surge," reflecting a profound rise in circulating catecholamines as a compensatory response to maintain cerebral perfusion pressure gradients in the context of elevated intracranial pressure. This autonomic surge is associated with significant histopathologic changes in the myocardium, electrocardiographic changes indicative of ischemia, and functional impairment of cardiac contractility. The failure of the autonomic surge to maintain cerebral perfusion pressure gradients results in herniation with spinal cord ischemia, brain death, and resultant vasodilation.

Key points 3.3 Sequential physiologic events associated with severe central nervous system injury leading to brain death

Autonomic surge that occurs in an effort to preserve cerebral perfusion

Impaired cardiac contractility

Herniation of the brain with spinal cord ischemia

Brain death and profound vasodilation

The importance of the autonomic surge in human donors was recently illustrated in a study that reported significant improvement in donor myocardial function when the autonomic surge was aborted

pharmacologically. Treatment with esmolol, uradipil, or nicardipine resulted in preservation of left ventricular ejection fraction and a higher rate of cardiac procurement. This study is cited solely to illustrate the potential impact of the catecholamine surge on the donor heart and not to advocate this as standard therapy.

The endocrine changes associated with brain death were first described by Novitzky and Cooper in a baboon model of brain death that results in a significant decrease in circulating thyroid hormones. Although well described in animal models, similar findings have been observed somewhat inconsistently in human organ donors. It has been proposed that the use of hormone resuscitation therapy consisting of thyroid hormone, steroids, insulin, and glucose facilitates the return of cardiac function and improves rates of procurement for all organs. Although frequently employed in donor management, hormone resuscitation therapy remains controversial and is discussed further.

To summarize, cardiovascular and hemodynamic management of the potential organ donor is complicated by the neurocardiac injury of the initial insult and the sequelae of physiologic events accompanying brain death. Optimal outcomes require aggressive management during the period immediately preceding brain death and in the period between brain death and declaration, and the securing of consent. The remainder of this section reviews a structured approach to the hemodynamic management of the potential organ donor.

Management algorithm

Figure 3.1 provides an overview of the cardiovascular and hemodynamic approach to the management of potential organ donors. All potential donors should be assessed for stability of mean arterial blood pressure, urine output, and extent of vasoactive support. Echocardiographic assessment of cardiac function is essential but interpretation of results depends critically on the timing of the studies as discussed below. In those potential organ donors achieving the stability thresholds identified in Figure 3.1, further cardiac assessment, sometimes including cardiac catheterization, should be undertaken if the donor is of suitable age and if procurement of the heart is being considered. As noted previously, many potential organ donors will have significant cardiac dysfunction. Echocardiographic studies performed immediately after brain death and before hemodynamic stabilization will likely reveal significant cardiac dysfunction.

The recent literature highlights the impact of echocardiographic assessment of left ventricular function on cardiac transplantation rates. In one study, 44% of potential heart donors did not have cardiac procurement. Echocardiographic abnormalities accounted for failure to procure hearts in 28% of cases and the odd ratio for failure of cardiac procurement increased by 1.4 for every 5% decrease in ejection fraction. It is important to emphasize that echocardiographic abnormalities do not always reflect histopathologic changes in the myocardium. In a recent echocardiographic study that evaluated 66 consecutive brain dead donors evaluated as heart donors, echocardiographic systolic dysfunction was evident in 42%. In those autopsied hearts that were not procured, there was a very poor correlation between the area of echocardiographic abnormality and the histopathology assessed at autopsy. Therefore, no heart should be excluded based on an initial echocardiogram. In a study that evaluated potential organ donors with ejection fractions <50% that were initially deemed not suitable for procurement, aggressive medical management was undertaken and resulted in 13 of 16 donors with an initial rejection procured with outcomes similar to ideal hearts.

Troponins are often used to evaluate cardiac suitability in potential organ donors because they are thought to reflect myocardial damage. Early studies strongly suggested that the presence of cardiac troponin concentrations was associated with significant cardiac dysfunction in the donor and caution was advocated about the use of donor hearts with elevated troponin levels. However, recent investigations have provided conflicting evidence. In a retrospective study that reviewed hearts accepted for transplantation, troponin levels were normal in 96 donors and elevated in 43 donors. This study reported that the recipients of hearts from donors with an elevated troponin level did not have a significant difference in the recipient need for circulatory support, nor was there any difference in short-term or longitudinal mortality. The authors concluded that minor troponin elevations were not associated with an

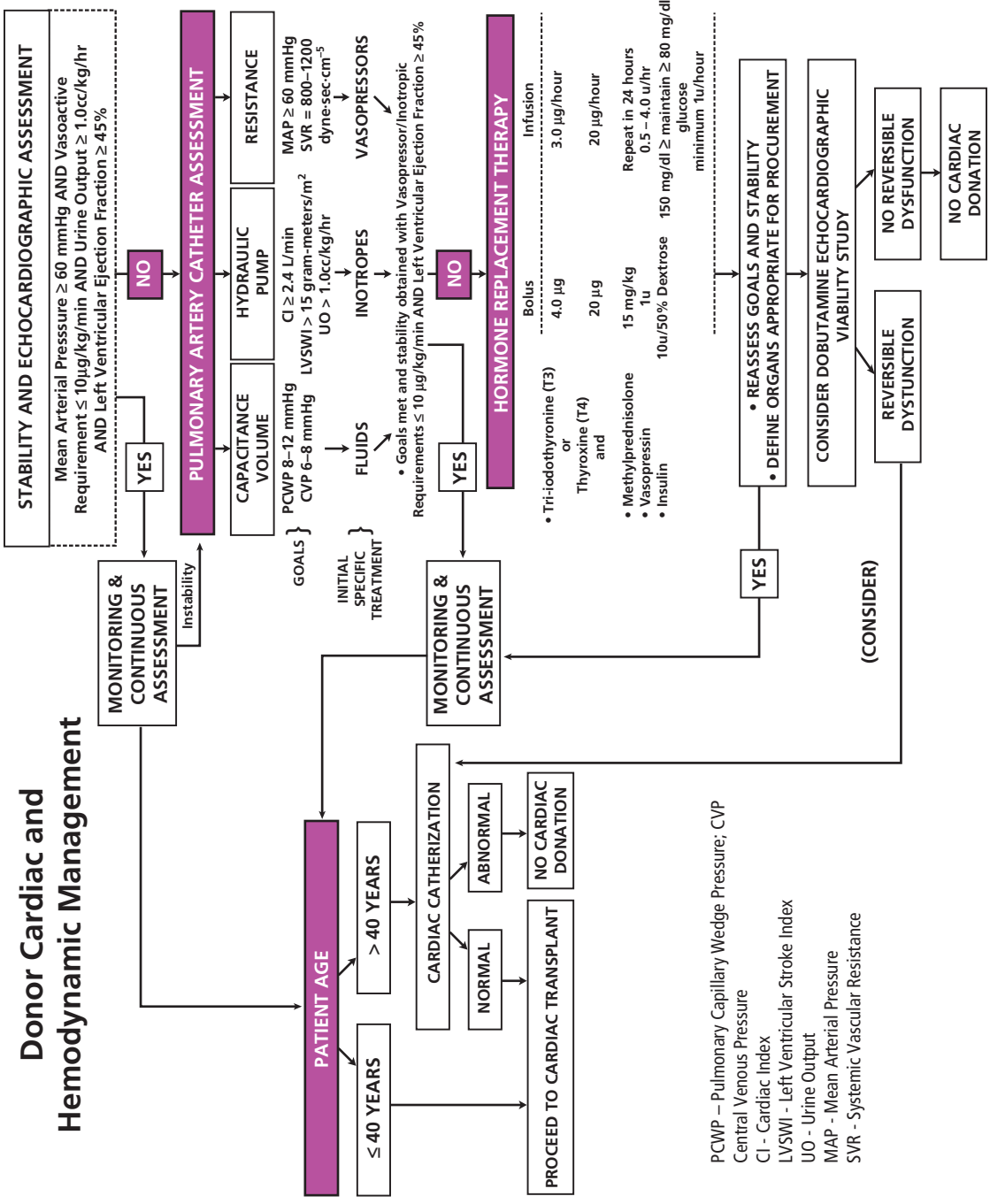

Figure 3.1 Algorithm for hemodynamic management of the deceased donor. Reproduced with permission of Massachusetts Medical Society.

increased risk of recipient mortality and suggested that potential heart donors should not be discarded based on troponin elevations alone.

Similar to the care of critically ill patients, an interdisciplinary approach employing the skills of intensivists, pulmonary and cardiac consultants, nurses, and respiratory therapists in concert with the OPO coordinator is strongly advocated. In one study, standardizing donor management through a protocol that relied on recommendations for general management, laboratory and diagnostic studies, and respiratory therapy during the continuum of referral, declaration, and consent resulted in a 10.3% increase per 100 donor organs recovered and a 3.3% increase in total organs per 100 donor organs transplanted. Similar dramatic improvements in the rates of organ procurement have been reported with the development of an organ donor management team dedicated to the aggressive management of potential organ donors. Utilizing an approach that consisted of early recognition of potential organ donor, a dedicated team involved in the medical management of the donor and aggressive resuscitation, the University of Southern California Trauma Intensive Care Team, reported that brain death-related complications had no effect on the number of organs donated. When comparing conventional donor management with an aggressive donor management team employing a standard protocol, multiple benefits were realized, including a significantly decreased number of donors lost from cardiovascular collapse and an increase in the number of organs recovered per donor.

Failure to achieve the stability thresholds identified in Figure 3.1 necessitates invasive monitoring to define the appropriateness of intravascular volume, cardiac function and the extent of vasodilation. The Canadian Counsel for Donation and Transplantation has recommended the following guiding principles for hemodynamic donor management:

- There should be clear recognition that intensivists characteristically titrate cardiovascular therapy to clinical, biochemical, and hemodynamic endpoints that ensure restoration and adequacy of intravascular volume without excess volume, and appropriate support of cardiac function and vascular tone to ensure optimal cardiac flow for organ perfusion.
- The use of vasoactive cardiovascular support assumes that intravascular volume has been adequately restored.
- Evaluation of cardiovascular function and hemodynamic status is a global measurement of multiple variables and no single measurement variable in isolation should dictate therapy.
- Escalation to include vasoactive support should be accompanied by an escalation in hemodynamic monitoring
- Key stability thresholds should serve as targets to guide therapy. However, rigid adherence to numbers should be balanced by the overall clinical evaluation of cardiovascular status similar to any other critically ill patient. Cardiovascular support should be based upon rational physiology with pure vasopressors (vasopressin, phenylephrine) distinguished from vasopressors with β agonists with inotropic action (norepinephrine, epinephrine).

As a consequence of therapies designed to minimize intracranial pressure elevations, the potential organ donor characteristically exhibits intravascular volume depletion, cardiac dysfunction, and vasodilation. Figure 3.2 depicts the differential diagnosis of hemodynamic instability in the potential organ donor. Hypovolemia is common secondary to the use of fluid restriction, diuretics, and mannitol. Diabetes insipidus and stress-induced hyperglycemic osmolar diuresis additionally contribute to decreased effective intravascular volume. These may be superimposed on the inadequate intravascular volume resuscitation, a capillary leak syndrome, or hypothermic diuresis. Cardiac dysfunction and vasodilation are usually coincident processes, primarily attributable to the brain death phenomenon, although other factors may contribute as depicted in Figure 3.2.

Fluid resuscitation

Fluid resuscitation should be based on an assessment of intravascular volume using measurement of either a central venous pressure (CVP) or pulmonary artery capillary wedge pressure (PCWP). Transfusion of packed red blood cells should be prescribed to maintain a hematocrit of at least 30% to promote oxygen delivery. Initial expansion of the intravascular volume when appropriate should be undertaken with 0.9% saline, even in the presence of hypernatremia. Subsequent to the correction of intravascular volume deficits and titration of fluid resuscitation to endpoints depicted in Figure 3.1, correction of hypernatremia should be undertaken using either Ringer's

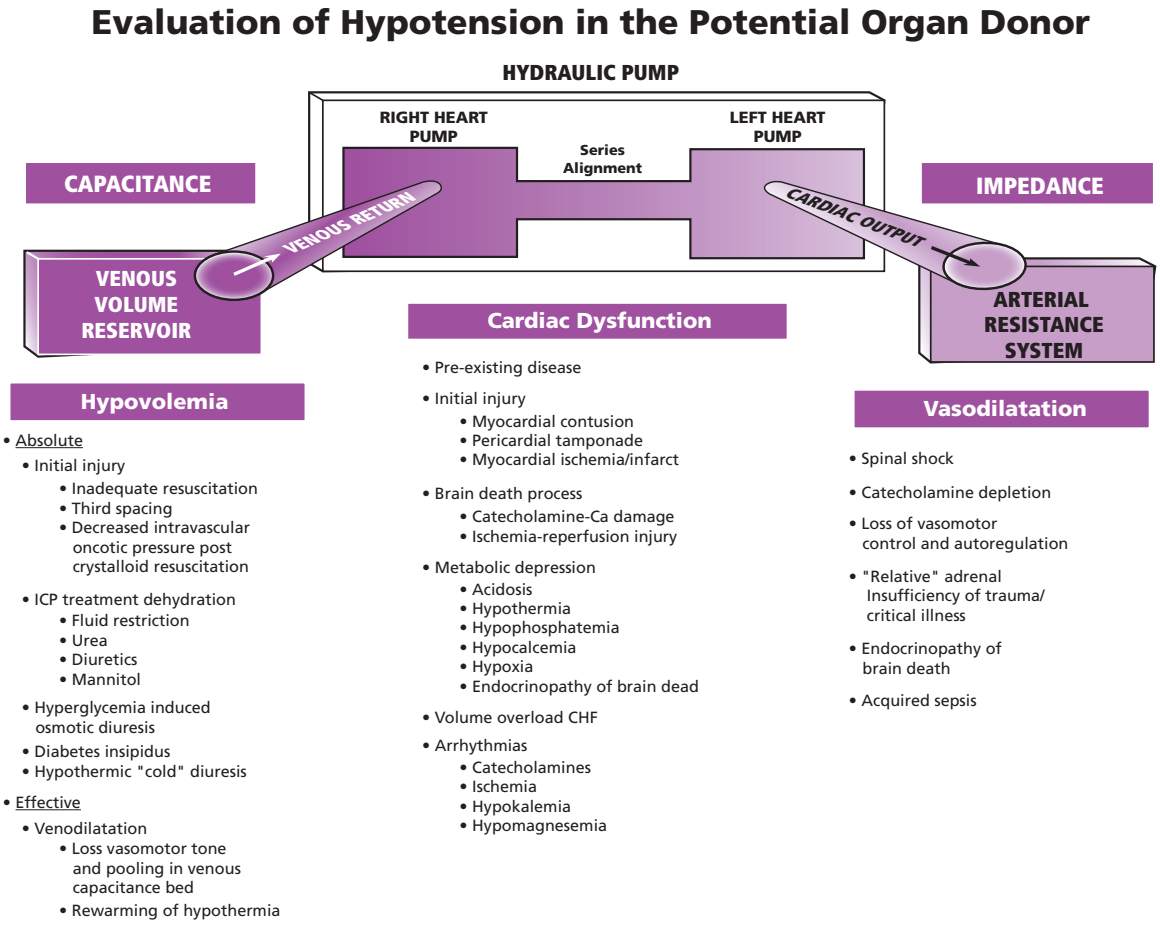

Figure 3.2 Pathophysiologic considerations in evaluating hypotension in a potential deceased donor. Reproduced with permission of Massachusetts Medical Society.

lactate solution or hypotonic saline. Given the frequent competing and antagonistic fluid resuscitation strategies related to lung and renal procurement, it is imperative to judiciously assess the adequacy of fluid resuscitation using endpoints of CVP or PCWP. Maintenance of renal function is facilitated by a more aggressive approach to volume resuscitation as case series have suggested that maintaining a urine output in excess of 100 mL/h in the hour before transplantation correlates with optimal postoperative renal function in the recipient. On the other hand, excessive fluid resuscitation against a background of brain death-induced changes in lung permeability may precipitate the accrual of extravascular lung water, jeopardizing lung suitability as the PaO_2/FiO_2 ratio becomes impaired and infiltrates appear on the chest radiograph. One of the most common reasons for failure to procure lungs is progressive pulmonary dysfunction consequent on excess resuscitation.

Vasoactive support

After the assessment of intravascular volume and titration of fluid resuscitation to the endpoints defined in Figure 3.1, many donors require vasoactive support. Previously, there was a reluctance to employ vasoactive support in the potential organ donor because of concerns that vasopressors might jeopardize organ function in the recipient. However, multiple recent series have reported negligible or non-existent associations between the level of vasoactive support in the donor and the outcome for the transplant recipient.

The putative adverse effects of catecholamines were most often reported in retrospective studies that provided inadequate details about assessment and normalization of intravascular volume. Indeed, recent investigations suggest that use of catecholamines may beneficially affect recipient renal function through their immunomodulatory effects on the inflammatory response. However, no firm recommendations regarding the specific vasoactive agent of choice can be made because randomized controlled trials are lacking. At this time, it would appear that therapy should be targeted and focused on the dominant physiologic abnormality. In cases of significant vasodilation, agents that promote vasoconstriction such as vasopressin, phenylephrine, or norepinephrine should be used. When the predominant physiologic abnormality is cardiac dysfunction, agents with greater inotropic support, such as dopamine or dobutamine, would be appropriate. Modulating and defining the specific combination of various agents are predicated upon variables derived from invasive monitoring or serial echocardiographic studies.

Hormone replacement therapy

Failure to achieve the predetermined thresholds identified in Figure 3.1 through the use of fluid resuscitation and vasoactive support warrants consideration for hormone replacement therapy (HRT). In the past, HRT was reserved for donors with ongoing hemodynamic instability. However, a recent large retrospective review of potential organ donors suggested that the combination of methylprednisolone, vasopressin, and thyroid hormone exerted a significant benefit for potential donors. The rate of organ procurement and corresponding organ transplantation was significantly higher in the HRT group. This same retrospective review concluded that cardiac recipient outcomes were dramatically improved by the use of HRT. It is important to recognize that these were retrospective and uncontrolled trials. HRT remains a controversial approach, which is best illustrated by the contrast in recommendations from two recent reviews of reported trials using HRT. One review concluded that routine administration of thyroid hormone in the management of potential organ donor was not warranted, although rescue replacement was deemed appropriate in some cases. In contrast, the review of Novitzky et al. (see Further reading) concluded that HRT results in dramatic improvement in cardiac function, enabling a greater rate of organ procurement. Insofar as there appear to be potential benefits and few adverse effects of HRT, it has become increasingly employed as a standard of practice in the early phases of organ donor management. Until randomized controlled trials provide guidance, it would seem appropriate to assess the need for HRT on a case-by-case basis.

Respiratory management

Respiratory management of the potential organ donor is frequently complicated by factors that result in lung procurement rates appreciably lower than those of other organs. Frequently, the pulmonary history of the patient is unknown and there may be underlying lung disease related to prior infections, occupational exposures, or use of tobacco that are not readily apparent on the presentation and initial evaluation of the donor. The causative event resulting in brain death, particularly when associated with trauma, is almost uniformly associated with aspiration and may be associated with pulmonary contusion. The period in the ICU further contributes to pulmonary dysfunction related to the complications of mechanical ventilation, including barotrauma, aspiration, hospital-acquired pneumonia, the effects of oxygen toxicity, and atelectasis.

The role of brain death in donor lung injury has traditionally been ascribed to neurogenic pulmonary edema. Consequent on the herniation process and the autonomic surge with high catecholamine levels, a blast injury to the pulmonary vasculature is proposed to initiate a transient massive hydrostatic pressure gradient that precipitates accumulation of alveolar fluid. Structural damage to the capillary endothelium similarly occurs secondary to the sympathetic activity. Recently, an intense inflammatory response has been described in which inflammatory cytokines activate endothelial cells to express adhesion molecules and mediate the production of interleukin-8 (IL-8). This neutrophil activator stimulates neutrophils and precipitates the release of reactive oxygen species and proteolytic enzymes that further enhance lung permeability.

The consequences of pulmonary donor inflammation have been well described by Fisher et al. (see

Further reading) in cases of non-traumatic brain death. Using open lung biopsy and bronchial alveolar lavage, they found that the concentration of neutrophils and IL-8 was dramatically higher in patients who sustained brain death compared with controls. Subsequent investigations correlated the extent of donor inflammation with recipient outcome and found a close correlation between the magnitude of the IL-8 expression and neutrophilic infiltration with graft function and recipient survival. This suggests that there is a preclinical injury to the lungs consequent on the brain death process and provides further evidence of the immunologic continuum between the donor and recipient.

The criteria for defining an "ideal" lung for transplantation were established early in the transplant era and have been criticized as arbitrary and capricious. These criteria generally include a PaO_2/FiO_2 ratio >300, a PEEP requirement <5 cmH_2O, a clear chest radiograph, age <55 years, tobacco use <20 pack-years, and the absence of trauma, surgery, aspiration secretions, malignancy, or infective-appearing secretions. Many lungs are precluded from procurement because of these stringent criteria. In a study that assessed lungs rejected for procurement because of pulmonary edema, the authors concluded that 41% of rejected lungs were potentially suitable for transplantation. Similar results were reported by Fisher et al. who compared the intensity of the inflammatory response in donors who were accepted to that of donors who were excluded by clinical criteria. Based on indices of inflammation, there was no difference between lungs that were accepted and those that were excluded, prompting the authors to conclude that the current selection criteria represented a very poor discriminator of pulmonary injury and that many lungs are unnecessarily excluded.

Although some lungs are able to maintain their ideal characteristics from brain death to procurement, many lungs are considered marginal. Marginality is traditionally defined as those lungs with a breech in the conventional criteria related to their baseline status, independent of problems acquired in the ICU. Lungs may also be characterized as marginal as a consequence of acquired and reversible processes in the ICU such as atelectasis, alveolar fluid accumulation, and aspiration. Newer respiratory and pulmonary management techniques have resulted in dramatic improvements in rates of lung procurement. In a study designed to maximize utilization of donor lungs for transplantation, Gabbay applied routine pulmonary and respiratory ICU management techniques consisting of manipulations of mechanical ventilation and PEEP, chest physiotherapy, ensuring appropriate fluid balance, and bronchoscopy in a pool of potential organ donors. In the population with an "unacceptable" PaO_2/FiO_2 ratio < 300, approximately 50% of the lungs were optimized and successfully procured. Marginal lungs constituted 57% of all transplantation preformed. The marginal and ideal lungs resulted in similar recipient outcomes, including postoperative gas exchange, ICU length of stay, and short- or medium-term mortality. Identical to an aggressive approach targeted at cardiac optimization of the potential donor, a structured and organized approach to managing the potential lung donor increases procurement of lungs.

Angel et al. (see Further reading) reported the impact of a lung transplantation donor management protocol on lung donation and recipient outcomes. Using a protocol strategy that included education and active donor management evaluation, the authors reported a dramatic increase in the rate of lung procurement. The educational initiative consisted of the transplant pulmonologist meeting with the OPO staff for training sessions on donor selection and management, emphasizing that all donors should be perceived as potential lung donors and that consent should be obtained for all organs. In addition, education was provided on donor management strategies. Active donor management consisted of ventilatory recruitment maneuvers, restriction of fluid administration, administration of diuretics, and implementation of techniques targeted at preventing aspiration. Alveolar recruitment was undertaken when the PaO_2/FiO_2 ratio was <300 or when pulmonary infiltrates, consistent with pulmonary edema or atelectasis, were present The alveolar recruitment strategy consisted of pressure control ventilation with an inspiratory pressure of 25 cmH_2O and a PEEP of 15 cmH_2O for 2 h.

After this period, the ventilatory mode was changed to a conventional volume control ventilation with a tidal volume of 10 mL/kg and a PEEP of 5 cmH_2O. Fluid balance was carefully monitored and a strategy, targeted at minimizing the use of crystalloid and adding diuretics to maintain a neutral to negative fluid balance, was incorporated into the protocol. The

risk of aspiration was diminished by elevating the head of the bed 30° and inflating the balloon to the endotracheal tube to 25 cmH_2O. Bronchoscopy was performed on all patients to evaluate radiographically detected areas of pulmonary infiltrates, contusions, or aspiration. This management process was continued until lung procurement. Using this strategy, the rate of lung procurement was dramatically higher in the protocol period (25% compared with 11%). This represented an estimated risk ratio of 2.2 in favor of the protocol, with significantly more patients receiving transplants during this period (121 vs 53). Importantly, 54% of the actual lung donors had initially been considered poor donors and these donors provided 52% of the 121 lung transplants performed. Similar to the Gabby study, the type of donor was not associated with a significant decrease in recipient survivorship or any other clinical metric of recipient graft function. As this study illustrates, aggressive management of the potential organ donor has clearly been shown to result in increased rates of lung procurement and transplantation.

Case

A 43-year-old man was declared brain dead after a gunshot wound to the head. He required vasopressin for severe hypotension. The chest radiograph suggested pulmonary edema with atelectasis of the left lower lobe. A Swan–Ganz catheter was placed to monitor PCWP. Pressure control ventilation was instituted for 2 h with and inspiratory pressure of 25 cmH_2O and PEEP of 15 cmH_2O. Thereafter, volume control ventilation was resumed with PEEP of 5 cmH_2O. Bronchoscopy was performed and suggested no evidence of infection. The chest radiograph improved dramatically and organs were harvested for heart, lung, and kidney transplants.

Donation after cardiac death

Donation after cardiac death was previously referred to as non-heart-beating organ donation and was the only means available for organ procurement during the early period of transplantation in the USA. With the advent of uniformly accepted criteria for determination of brain death, many transplant centers stopped procuring organs from DCD donors and focused exclusively on the procurement of organs from brain-dead donors. Given the period of warm ischemia time that occurs in DCD, procurement from brain-dead donors was preferable because of improved organ function. Given the ongoing shortage of transplantable organs, there has been a resurgence in procurement from DCD donors. Currently, all OPOs are mandated from the federal government to work with their referring hospitals to establish formal DCD policies and protocols.

The issue of donation after cardiac death has been addressed by the Institute of Medicine which concluded that the procurement of organs from non-heart-beating donors is appropriate, effective, and an ethically accepted approach to secure transplantable organs. The Institute of Medicine stipulated that written protocols for the procedure should be openly available and transparent, that the process define separate responsibilities for the attending physician and transplant procurement physicians, that families be fully informed and offered the option of the withdrawal of life support, and that donors and families not suffer financial penalties. It was further suggested that the use of anticoagulants and vasodilators be used on a case-by-case basis and that the determination of death should be defined by cessation of cardiopulmonary function for at least 5 min by electrocardiographic and arterial pressure monitoring.

It is absolutely crucial that the decision to withdraw life-supporting therapy be made independent and before any initiation of discussions related to organ and tissue donation. Once the decision has been made to forego further life-sustaining therapy, it is appropriate to initiate the discussion and provide the family with the opportunity for donation after cardiac death. At this point, integrating the OPO into the discussion is appropriate. The overwhelming majority of DCD donors have a devastating neurologic injury although, occasionally, a subset of patients with non-neurologic injuries has become DCD donors. The withdrawal of support in the case of a DCD donor should be identical to the withdrawal process used for any other patient. Ensuring that the patient is comfortable, similar to the approach used in any other circumstance of withdraw care, is of paramount importance. The use of anticoagulants and vasodilators during this process should be made on a case-by-case basis with the family fully informed throughout the entire process. Throughout the withdrawal phase, blood pressure, oxygenation, and urine output are monitored in an effort to define the

duration of warm ischemia. In general, the time from extubation/withdrawal of support that enables viable organs for transplantation is approximately 1 h. Further prolonged periods between extubation/withdrawal of therapy lead to hypotension and organ ischemia that effectively preclude the use of organs for transplantation. The withdrawal process may occur in the patient's room or the patient may be transferred to the operating room. Death is pronounced using cardiopulmonary criteria after a 5-min period of asystole and electrocardiographic silence. Organ recovery is subsequently initiated after pronouncement of death.

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